REMARKS

Claims 1-5 are pending for examination.

Rejections Under 35 U.S.C. §101

Claims 1-5 were rejected on the assertion that the claimed invention lacks utility. With respect to Applicants' arguments that the PTO has withdrawn the utility rejections in applications having similar disclosures, the Examiner asserts that each case must be decided on its own merits.

The Examiner asserts that Applicants have not provided any testing of the expression of the PRO1864 polypeptide and that one skilled in the art would not know if the change in PRO1864 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO1864 polypeptide expression would change in cancer. According to the Examiner, the fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist.

The Examiner asserts that Mr. Grimaldi's Declaration is unpersuasive because it does not provide anything specific concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. In addition, the Examiner asserts that although the Grimaldi Declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues, this statement is in contrast to the specification's teachings.

According to the Examiner, given the asserted paucity of information regarding PRO1864 mRNA expression and the asserted lack of data concerning PRO1864 polypeptide expression, Hu is evidence that a skilled artisan would consider the precise level of PRO1864 gene expression as relevant. With respect to the Kuo reference submitted by the Applicants, the Examiner asserts that it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data.

With respect to Applicants' arguments regarding the accuracy of data from pooled samples, the Examiner asserts that without knowledge of the degree of variation within the pool

one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue.

The Examiner also cites the decision in *Bindra v. Kelly* ((206 USPQ 570 (BPAI 1979)) for the proposition that a strong probability of utility is not sufficient to establish practical utility. In addition, the Examiner continues to maintain his position that the present invention lacks utility because there are numerous mechanisms for regulating protein synthesis.

The Examiner asserts that the Declaration by Dr. Scott is unpersuasive because it is based upon microarray data, which the Examiner asserts has been disparaged as being inaccurate, and because it does not provide specific data concerning PRO1864 mRNA or protein expression. The Examiner also asserts that the second Polakis Declaration is unpersuasive because it does not provide specific data concerning PRO1864 mRNA or protein expression. In addition, the Examiner asserts that the skilled artisan would not know if PRO1864 polypeptide expression would change in cancer because, according to the first Polakis Declaration, in at least 20% of the instances examined there was no correlation between mRNA and protein. The Examiner also asserts that the second Polakis Declaration indicates that 10% of the cases examined do not show a correlation between mRNA and protein.

Applicants continue to maintain that, for the reasons of record, the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1864 polypeptide is expressed at least two-fold higher in melanoma compared to normal skin tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase;

3. Given the differential expression of the PRO1864 mRNA in melanoma, it is more likely than not that the PRO1864 polypeptide is also differentially expressed in melanoma, making the claimed antibodies useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that one skilled in the art would not know if the change in PRO1864 mRNA levels is tumor-dependent or tumor-independent and that, without knowledge of the degree of variation within the pooled samples, one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue.

2. The PTO asserts that Applicants have not provided specific data demonstrating that the PRO1864 polypeptide is differentially expressed in melanoma.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the PRO1864 Polypeptide Meets the Utility Requirement

Applicants note that the PTO has concluded that the PRO1864 polypeptide possesses sufficient utility to satisfy 35 U.S.C. §101. In particular, in the Office Action mailed November 2, 2006 in U.S. Patent Application 10/063,518, which claims the PRO1864 polypeptide and which contains the same data in Example 18 as the present application, the

Examiner withdrew the previously asserted utility and enablement rejections. The Examiner stated:

> Applicants assert that the expression levels of protein correlate to mRNA (cDNA) levels when the cDNA is measured by quantitative PCR (i.e. RT-PCR). Applicants have provided more than 140 references in support of this position. The prior art of record (Haynes et al., Gygi at al., Gökmen-Polar, Greenbaum, Lian, Fessler, etc.), argued by the Examiner, is not specifically directed to message levels measured by RT-PCR. Based on the totality of evidence of record, one of skill in the art would find it more likely than not that an increase in message as measured by RT-PCR would be predictive of an increase in protein expression levels, absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of the nucleic acid encoding PRO1864, also supports a conclusion of differential expression of the PRO1864 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1864 polypeptide diagnostically for distinguishing melanoma from normal skin, as asserted by Applicants.

In addition, as previously submitted, the PTO has also concluded that "one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels" in several other applications that rely on *data from the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility. (See *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583). In view of the PTO's recognition of the utility of the PRO1864 polypeptide and the foregoing arguments, as well as the arguments previously submitted, Applicants respectfully request that the PTO withdraw the present utility rejection.

Duty of the Examiner in Examination of an Application

Applicants respectfully remind the Examiner that he has a duty to consider and respond to Applicants' arguments in an attempt to clarify the issues in dispute:

> The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal. *M.P.E.P. §706.07* (emphasis added).

Applicants have attempted to respond to each of the Examiner's previous arguments, pointing out what the Applicants view as the factual errors or flaws in the Examiner's reasoning.

Applicants respectfully request that the Examiner respond to Applicants' arguments in an attempt to clarify the issues in dispute prior to appeal.

The Data Reporting Differential Expression of PRO1864 mRNA are Sufficient to Provide Utility for the mRNA as a Diagnostic Tool

Applicants next address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1864 polypeptide in melanoma is insufficient. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1864 gene is more highly expressed in melanoma compared to normal skin tissue and is therefore useful as a diagnostic tool for melanoma. This assertion is based on the results of RT-PCR analysis of pooled normal skin tissue and pooled melanoma tissue using methods that are well-established in the art.

This utility is substantial, *i.e.* distinguishing tumor cells from normal cells is not an insubstantial or trivial utility without a real world use, and it is specific, *i.e.* it is directed to specific disease and is not a utility that the entire class of nucleic acids shares. Finally, this asserted utility is credible, as one of skill in the art would readily believe that a nucleic acid sequence can be used as a marker to distinguish tumor tissue from normal tissue.

Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true. The Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement. M.P.E.P. §2107.02, "Procedural Considerations Related to Rejections for Lack of Utility," states:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. *M.P.E.P. §2107.02* at III. A., *quoting In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (C.C.P.A. 1974) (emphasis in original).
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> Thus, *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. ... Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. ...

> Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. *Id.*

With respect to the use of the PRO1864 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility." Therefore, the question is whether the PTO has established that there is a reason to doubt the objective truth of Applicants' assertion that using standard RT-PCR procedures to examine the expression of the PRO1864 mRNA in pooled normal skin tissue and pooled melanoma tissue samples, Applicants discovered that PRO1864 mRNA is differentially expressed between normal and tumor tissue such that it can be used as a diagnostic tool.

In asserting that Applicants' disclosure of differential expression of the PRO1864 mRNA is insufficient, the PTO states that "Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of the expression of the PRO1864 polypeptide." *Office Action* at 5. Applicants maintain that, just as desirable pharmaceutical properties in a standard animal model are sufficient to confer utility on a chemical compound because such animal models are generally indicative of results in humans, the demonstration of differential mRNA expression is sufficient to confer utility on antibodies which bind to the encoded polypeptide because differential mRNA expression is generally indicative of differential expression of the encoded polypeptide, which renders the antibodies useful as a diagnostic tool. See *In re Brana,* 34 U.S.P.Q.2d, 1436 (Fed. Cir. 1995). In *In re Brana*, the court found that the PTO's references discussing the predictive value of the animal testing performed by the Applicants were not sufficient to show that one skilled in the art would reasonably doubt the asserted utility of the claimed compounds. *Id.* at 1441. Applicants maintain that, just as the PTO was unable to demonstrate a lack of utility by asserting that the animal testing conducted by the applicants in *In re Brana* was insufficiently predictive of the utility, the PTO's assertions regarding the predictive value of a demonstration of differential mRNA expression are

insufficient to demonstrate that the claimed antibodies lack utility. Thus, Applicants continue to maintain that, in view of the general correlation between differential mRNA expression and differential expression of the encoded polypeptides, Applicants' showing of differential expression of the PRO1864 mRNA would lead one skilled in the art to reasonably believe that the PRO1864 polypeptide is differentially expressed, thereby demonstrating the utility of the claimed antibodies.

Applicants note that whether or not an application discloses a utility for a claimed invention is a question of fact. See *In re Fisher*, 421 F.3d 1365, citing *In re Ziegler*, 992 F.2d 1197 (Fed. Cir. 1993). Any assertion that the claimed invention lacks utility must be supported by substantial evidence. *Id.* at 1369; *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Applicants maintain that the PTO has not provided substantial evidence that the claimed invention lacks utility. In fact, the PTO's heightened utility requirement is unsupported by any evidence whatsoever. The PTO provides no evidence or findings of facts to suggest that one skilled in the art would doubt Applicants' disclosed differential expression. Based on the complete failure to present any evidence whatsoever to bring into question Applicants' disclosed differential expression, Applicants submit that the PTO's heightened requirements for evidence are improper and insufficient to overcome Applicants' presumption of utility.

In addition to questioning the correlation between differential mRNA expression and differential expression of the encoded polypeptide, the PTO also questions the reliability of Applicants' data showing differential mRNA expression. Applicants have submitted considerable evidence demonstrating the reliability of the data in Example 18 and the correlation between differential mRNA expression and differential expression of the encoded polypeptide. For example, Applicants previously submitted a copy of a first Declaration of J. Christopher Grimaldi. Paragraphs 6 and 7 of Mr. Grimaldi's first Declaration establish that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. Mr. Grimaldi also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," and that the samples were made from pooled samples of tumor and corresponding normal tissue, increasing the accuracy of the data, thus establishing their reliability. *See Grimaldi Declaration* at ¶¶ 5 and 7. In addition, he

explains that, contrary to the PTO's assertions, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." *Grimaldi Declaration* at ¶7. Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant, as is the baseline level of expression. As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." *Id.*

The Examiner asserts that one skilled in the art would not know if the change in PRO1864 mRNA levels is tumor-dependent or tumor-independent and would not know if or how PRO1864 polypeptide expression changes. In addition, the Examiner maintains that without knowledge of the degree of variation within the pooled samples, one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue.

Applicants maintain that, as discussed in Mr. Grimaldi's first Declaration, pooled samples provide a more accurate indication of whether an observed change is tumor-dependent than individual samples because the observed extent of differential mRNA levels between tumor tissue and normal tissue is normalized to reflect the typical degree of variation within the pool. As previously pointed out, should there be a particular sample in the pool which exhibits an atypical degree of variation between tumor tissue and normal tissue, the effects of that sample on the observed degree of variation are mitigated by the other members of the pool. Accordingly, the observation of differential mRNA expression in tumor tissue compared to normal tissue using pooled samples is a reliable indication that such differential expression is in fact disease dependent.

With respect to the Kuo reference submitted by Applicants to point out the irrelevance of the microarray-based data presented in the Hu reference previously cited by the Examiner, the Examiner asserts that from the evidence provided it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. According to the Examiner, there is no basis for asserting that microarrays are simply not relevant to Applicants' RT-PCR data.

This response does not address Applicants' arguments regarding Hu. Applicants have not asserted that Kuo's microarray data is consistent with Kuo's PCR data. Whether it is consistent

or inconsistent is irrelevant to Applicants' argument, which is that those of skill in the art recognize that data generated by RT-PCR is more reliable, sensitive and accurate than microarray data. Kuo supports this assertion by stating in comparison to microarrays: "Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction...." One does not need to know if Kuo's RT-PCR data was consistent with Kuo's microarray data to rely on this statement any more than one needs to know what data Hu is relying on for the statements quoted by the Examiner – the Examiner cannot rely on the unsupported opinion of Hu, and then reject Kuo's statement because it allegedly lacks support.

In addition, Kuo is not cited to provide a basis for doubting Hu's statements. While Applicants do question the truth of Hu's unsupported opinions, the accuracy of their statements is of no relevance because they are discussing microarray data, not pooled sample RT-PCR data as in the instant application. Therefore, Hu's statements cannot support a rejection of Applicants' pooled sample RT-PCR data. The Examiner must explain how opinions regarding microarray data, even if true, are applicable to pooled sample RT-PCR data, given Applicants' assertions and supporting evidence that one of skill in the art would recognize RT-PCR as more reliable, sensitive and accurate. Applicants continue to maintain that, until the Examiner provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often "attributable to disease-independent differences between the samples," the Examiner's rejection of the data in Example 18 based on Hu is unsupported and without merit.

The Examiner asserts that the statements in the first Grimaldi Declaration that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues, are in contrast to the specification which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0530.

This argument is not responsive as it does not indicate how the use of pooled samples of tumor tissue and pooled samples of corresponding normal tissue is inconsistent with or in contrast to the specification which states: "Identification of the differential expression of the

PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject." *Specification* at ¶[0530] (emphasis added). Nor does this response indicate what the relevance of this alleged "contrast" is to determining utility. It is incumbent upon the Examiner to explain how these statements are "in contrast" and what the relevance of the "contrast" is to Applicants' asserted utility so that Applicants can address this issue on appeal.

The Examiner asserts "In the present case, the declaration does not provide anything specific concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. It is unknown what level of difference is being reported or how many samples were tested. Given the paucity of information regarding PRO1864 mRNA expression and the complete lack of data concerning PRO1864 polypeptide expression, Hu is evidence that a skilled artisan would consider the precise level of PRO1864 gene expression as relevant." *Office Action* 7-8.

This argument is not responsive to Applicants' previous arguments. First, Hu teaches nothing at all regarding developing diagnostic markers of cancer. Second, Hu does not discuss the precise level of mRNA expression, but instead discusses relative differences such as 2-fold, 5-fold or 10-fold. *See Hu* at Abstract. Rather than supporting the Examiner's arguments, Hu supports Grimaldi's statement that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." Therefore, the Examiner has yet to explain how Hu supports his assertion that the precise level of gene expression is required, rather than the relative difference between tumor and normal tissue as asserted by Grimaldi. Applicants request that the Examiner clarify his position to simplify the issues on appeal.

To the extent that the Examiner is attempting to argue that based on Hu that one of skill in the art would consider the precise level of the relative difference (e.g. 2-fold, 5-fold, or 10-fold) important, Applicants have previously addressed why Hu's statements regarding 2-fold changes in microarray data are not relevant to Applicants' pooled RT-PCR data.

Essentially, the Examiner's entire argument can be summarized thus:

> The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist. The specification does not establish if the disclosed change in PRO1864 mRNA expression is one of those cases where there is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior. *Office Action* at 6.

Applicants have presented overwhelming evidence that changes in mRNA generally lead to changes in the corresponding level of the encoded protein, including the declarations of three experts in the field, and over 100 references which directly or indirectly support this position.

Were the Examiner to acknowledge that based on the record, Applicants have established that there is such a general rule or correlation, rather than stating that there "may be", the remaining issue regarding the Examiner's argument above would be whether the Applicants can rely on a general rule with admitted exceptions to provide utility, or if Applicants must provide specific evidence of the PRO1864 polypeptide expression. The Examiner apparently believes that if there is any exception to a correlation relied on for utility, a doubt is raised regarding the utility since it is not known if the claimed molecule follows the rule or the exception, and therefore specific direct evidence of utility is required. Applicants assert that a correct reading of the utility standard articulated by the Courts and the PTO indicate that the correlation does not need to be absolute or exact, but only reasonably indicative of the asserted utility. *See Nelson v. Bowler*, 626 F.2d 853, 856-57; *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564. Applicants could then appeal this issue to the Board of Patent Appeals and Interferences for clarification.

Therefore, in an attempt to clarify the issues in dispute, Applicants request that the Examiner acknowledge that based on a careful consideration of the ***entire record***, Applicants have established by a preponderance of the evidence (*i.e.* more likely than not) that those of skill in the art recognize that changes in mRNA level for a particular gene generally, but not always, lead to a change in the level of the encoded protein. Doing so would simplify issues for appeal.

The Declaration of Dr. Scott

To support their assertion that a change in mRNA level generally leads to a corresponding change in the encoded protein level, Applicants previously submitted the declaration of Dr. Randy Scott. The Examiner responds by arguing:

> The declaration under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 1-5. Dr. Scott bases his conclusions on microarray data, which Applicants have disparaged as inaccurate and unreliable. Further, Dr. Scott does not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to first and second Polakis declarations and because there are some exceptions on an individual gene basis, according to the Scott declaration. Neither the specification nor any of Applicants' arguments or other evidence establish if the disclosed change in PRO1864 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior. *Office Action* at 15.

Applicants emphasize that they have not "disparaged as inaccurate" microarray data. Applicants have merely argued that conclusions regarding "disease-independent" differences between samples based on microarray data cannot be extended to RT-PCR data because those of skill in the art recognize that the latter is more accurate, reliable, and sensitive than microarray data.

As to the remainder of the Examiner's argument – that because there are exceptions to the relationship between changes in mRNA and changes in protein, Applicants must provide actual testing of PRO1864 polypeptide – Applicants note that the Scott Declaration states exactly the opposite. Dr. Scott, an independent expert in the field of molecular diagnostics, states:

> [I]t has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified … **without the need to directly measure individual protein expression levels**. *Scott Declaration* at ¶10 (emphasis added).

Dr. Scott's declaration directly contradicts the personal opinion of the Examiner, and the Examiner has not given any reason to reject the Scott Declaration, other than the inaccurate statement that Applicants have disparaged microarray data. Without basis, the Examiner is ignoring the declaration of an independent expert in the field who states that one of skill in the art would rely on a correlation between changes in mRNA to predict changes in protein, in spite of the exceptions to the general correlation, without directly measuring the individual protein expression.

The Examiner has not explained his basis for rejecting Dr. Scott's opinion – he merely repeats the arguments made before the Scott Declaration was submitted. Applicants remind the Examiner that case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record **anew**. *See in re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). As the Examiner has previously stated, when considering the weight to be given an expert opinion, the Examiner should evaluate, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

(1) The nature of the fact sought to be established: The nature of the fact to be established is whether one of skill in the art would believe that differential mRNA levels reflect differential protein levels, such that they would rely on this general correlation to predict changes in protein by measuring changes in mRNA without directly measuring the individual protein expression. The nature of this question is such that it is best answered by those who are actually practicing scientists in the field of molecular and cancer biology, like Dr. Scott.

(2) The strength of any opposing evidence: The Examiner has not submitted any opposing evidence. The Examiner continues merely to rely on a few references which he asserts establish that there are exceptions to the general correlation between changes in mRNA and changes in protein. Although Applicants dispute the relevance of the Examiner's evidence, they have acknowledged that exceptions exist. However, the fact sought to be established is not whether exceptions to the rule exist, but rather, whether the correlation between Applicants'

evidence of utility and the asserted utility is well-established enough that one of skill in the art would accept Applicants' asserted utility based on the PRO1864 RT-PCR mRNA data. The Examiner has not presented any evidence that those of skill in the art would not rely on differential RT-PCR mRNA data to predict protein expression for diagnostic utility.

(3) The interest of the expert in the outcome of the case: Dr. Scott is an independent expert in the field. He is not an employee of the Assignee, nor is he an inventor of the instant application.

(4) The presence or absence of factual support for the expert's opinion: Dr. Scott relies on his extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels. In addition, Dr. Scott's conclusions are supported by the declarations of two other experts in the field, and over 100 other supporting references which Applicants have submitted.

When the factors outlined above are considered as a whole, it is clear that the Scott Declaration cannot simply be summarily dismissed. Applicants respectfully request that the Examiner properly consider the Scott Declaration, and articulate a proper basis for rejecting Dr. Scott's independent expert opinion – merely repeating the Examiner's personal opinion that one of skill in the art would require actual testing of the molecule is not a sufficient basis to reject the opinion of an expert in the field to the contrary, especially given the other evidence of record (3 expert declarations and over 100 references) which support Dr. Scott's conclusions.

The Declarations of Dr. Polakis

Applicants have submitted a second declaration of Dr. Polakis, including data for evaluation by the Examiner. In response, the Examiner argues:

> The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. ...*Office Action* at 17.

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> The facts to be established are whether or not the disclosed change in PRO1864 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO1864 transcripts and a corresponding change in PRO1864 polypeptides levels. The declarations do not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue....*Office Action* at 18.
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> Both the first and second Polakis declarations indicate that the data was generated using microarray analysis, which Applicants have disparaged as inaccurate and unreliable... Even if the Examiner were to assume that the disclosed change in PRO1864 transcripts could reasonably be correlated with an assumed change in PRO1864 polypeptide expression, it still could not be ascertained if the assumed change in PRO1864 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO1864 transcripts is disease-dependent or disease-independent. Even if the Examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO1864 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation, according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations. *Office Action* at 18-19 (emphasis added).

Applicants again emphasize that they have not "disparaged as inaccurate" microarray data. Applicants have merely argued that conclusions regarding "disease-independent" differences between samples based on microarray data cannot be extended to RT-PCR data because those of skill in the art recognize that the latter is more accurate, reliable, and sensitive than microarray data.

The Examiner continues to rely on his personal opinion that because there are exceptions to the general correlation, one of skill in the art would not rely on differential PRO1864 mRNA expression data to predict PRO1864 protein expression. The Polakis, Grimaldi, and Scott Declarations, all by experts in the field, state that the correlation is sufficiently reasonable that

one of skill in the art would rely on differential mRNA expression data to predict protein expression.

Applicants offer the Scott, Grimaldi, and Polakis Declarations, not to unequivocally prove that PRO1864 polypeptide is differentially expressed, but rather to prove that one of skill in the art would be more likely than not to believe that because the PRO1864 mRNA as measured by RT-PCR is differentially expressed, the PRO1864 polypeptide will likewise be differentially expressed. Applicants do not need to provide direct evidence of PRO1864 polypeptide expression to establish the asserted utility. Indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856-57, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564. In light of the proper utility standard, it is improper for the Examiner to reject the Polakis Declaration because it does not provide direct evidence of differential PRO1864 polypeptide expression – that is not what the Polakis Declaration is required to do. Instead, the Polakis Declaration is evidence that Applicants' evidence of utility is sufficient to convince one of skill in the art that the asserted utility is more likely than not true.

Applicants request that the Examiner acknowledge that there are cases where direct evidence of utility is not required because there is a reasonable correlation between the asserted utility and the evidence provided. In such cases, declarations establishing the reasonableness of the correlation between the asserted utility and the evidence provided, as well as reliance thereon, are probative. While the Examiner may not agree that this is one of those cases, such an acknowledgement would place the Polakis Declaration in the proper perspective – evidence that one of skill in the art would rely on differential mRNA data to predict protein expression – rather than viewing it as insufficient because it does not contain direct evidence of PRO1864 polypeptide expression.

The Examiner's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the Examiner takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO1864 polypeptide in

tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

In response to Applicants' position, the Examiner makes the following arguments:

> In the absence of any information on the role, activity or expression of the PRO1864 polypeptide in cancer, the Examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported change in PRO1864 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO1864 polypeptide expression would change in cancer. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist. The specification does not establish if the disclosed change in PRO1864 mRNA expression is one of those cases where there is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1864 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1864 polypeptide and claimed antibodies thereto. *Office Action* at 5-6.
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> However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. Therefore, Applicants argue that the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." Applicants' arguments have been fully considered but they are not persuasive. The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. *Office Action* at 16-17.

The Examiner also cites *Bindra v. Kelly* 206 USPQ 570 (Bd. Pat. Inter. 1979) for the proposition that "A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be 'foretold with certainty.' *Office Action* at 13. In *Bindra*

v. Kelly, the issue was whether Kelly could show the utility required for an actual reduction to practice in the context of an interference by demonstrating preparation of a first intermediate compound (Compound I) which could be used to prepare a second intermediate compound (Diol III) known to be useful in the synthesis of a known pharmaceutical. In particular, the issue was whether Kelly's preparation of Compound I coupled with the existence of a chemical reaction likely to convert Compound I into Diol III was sufficient to demonstrate utility. The Board concluded that Kelly had not demonstrated utility because "Practical utility can...be established only by an actual testing therefore, or by establishing such facts as would be convincing that such utility could be 'foretold with certainty.' *Bindra v. Kelly* 206 USPQ 570, 575 (Bd. Pat. Inter. 1979), quoting *Blicke v. Treves,* 112 USPQ 472, 475 (CCPA, 1952).

However, the *Bindra v. Kelly* decision notes several instances where a direct demonstration of utility was not required. In particular, *Bindra v. Kelly* notes that a direct demonstration of utility was not required in *In re Folkers and Shunk*, 145 USPQ 390 (CCPA 1965), *Breen v. Miller*, 146 USPQ 1539 (CCPA 1965), *Kyrides v. Bruson*, 41 USPQ 107 (CCPA 1939), *Richardson v. Cook*, 170 USPQ 86 (CCPA 1971), and *Ciric v. Flanigen*, 185 USPQ 103 (CCPA 1975). With respect to the foregoing decisions, the Board stated:

> Except for the particular situation in Kyrides, in all cases where the court did not find "obvious" utility, *significant* properties of the compositions were contemporaneously uncovered and appreciated. Thus, in Folkers, where an ex parte appeal from an examiner's rejection urging lack of adequate disclosure of utility was involved, it was disclosed by Folkers that the novel compounds, benzoquinones, had "activity similar [to certain compounds] isolated from beef heart mitochondria * * * [involving] electron transport activity of the mitochondria" and thus would necessarily have the same substantial utility as those certain compounds. In Breen v. Miller, the material of the counts had the *property* of being able to be drawn in to a fiber which sufficiently resembled other known fibers. In Richardson v. Cook, 170 USPQ at 87, the court found that the comtemporaneously demonstrated property of "stability" of a certain antiknock composition, containing known antiknock compounds, established utility. In Ciric v. Flanigen, 185 USPQ at 106, it was found that the contemporaneously demonstrated ability of the zeolites of the counts to undergo certain ion exchanges was sufficiently similar to known zeolites to establish utility. (Note the discussion of Breen and Folkers in Ciric). In the remaining cases cited herein concerning this issue, no such significant properties were found and we find none here.

As an initial matter, Applicants maintain that a showing of differential mRNA expression constitutes a disclosure of "significant properties" of the claimed antibodies and that, accordingly, no further demonstration of utility is required.

In addition, Applicants note that the decision in *Bindra v. Kelly* is inconsistent with later decisions. For example, as noted in M.P.E.P. §2138.05 VIII, *Bindra v. Kelly* is inconsistent with *Nelson v. Bowler,* 206 U.S.P.Q. 881 (C.C.P.A. 1980), in which a reasonable correlation between the observed properties and the suggested uses of an invention was found to be sufficient to establish utility. Furthermore, as previously noted, in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) there were exceptions to the correlations relied on for the asserted utility. In each of these decisions, the court concluded that the Applicants had demonstrated utility despite these exceptions.

Applicants maintain that the Examiner's analysis is flawed. According to the Examiner's analysis, because the in vitro screens and preliminary tests in *Nelson v. Bowler*, *Cross v. Iizuka*, and *Fujikawa v. Wattanasin* did not always correlate with the asserted utility, one of skill in the art would have a reason to doubt the asserted utility, and actual direct proof of the asserted utility would be required.

The Examiner's position was rejected by the courts – the courts did not require direct proof of the asserted utility even where there was evidence of exceptions to the general correlation relied on by the applicants: "Of course, it is possible that some compounds active *in vitro* may not be active *in vivo.* But, as our predecessor court in *Nelson* explained, a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices." *Fujikawa*, 93 F.3d at 1565 (emphasis added).

Contrary to the Examiner's assertion that "there is no reason for a skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior," Applicants have provided the Declarations of three experts in the field, and over 100 supporting references. This evidence establishes that one of skill in the art would be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic utility, and case law establishes that this is sufficient. Thus, the Examiner's position is untenable in light of the

evidence of record and relevant case law – exceptions to the correlation relied on for utility does not result in a requirement for direct evidence of the asserted utility.

Applicants' respectfully request that the Examiner reexamine his contention that only direct evidence of PRO1864 polypeptide expression can provide the required evidence of utility:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

Conclusion

Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1864 mRNA is differentially expressed in melanoma compared to normal skin tissue, the PRO1864 polypeptide will likewise be differentially expressed in melanoma. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1864 polypeptide establishes the claimed antibodies useful as diagnostic tools for cancer, particularly melanoma. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The Examiner maintains his rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph. Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Thus, since the enablement rejection is based on the rejection of the claims as lacking utility, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Priority

The Examiner asserts that the priority date of the present application is August 24, 2000. According to the Examiner, priority is not granted to U.S. Provisional Patent Application

60/170,262 because this application does not disclose the quantitative PCR analysis measuring PRO1864 mRNA levels.

Applicants continue to maintain that the present application is entitled to a priority date of December 9, 1999, the filing date of U.S. Provisional Patent Application 60/170,262.

Rejections Under 35 U.S.C. §102(e)

Claims 1-5 were rejected under 35 U.S.C. §102(e) on the assertion that they are anticipated by Tang et al. (WO 01/53312). According to the Examiner, Tang et al. disclose a polypeptide that is identical to the polypeptide of SEQ ID NO:14 and antibodies to the polypeptide, including monoclonal and humanized antibodies as well as antibody fragments and labels.

Applicants note that Tang claims priority to U.S. Patent Application 09/488,725, filed January 21, 2000. Applicants have obtained a copy of this patent application and note that it discloses a raw nucleic acid sequence and states that it is "similar to MLN64" and "similar to I38027 (PID: g2135214)". (See U.S. Patent Application 09/488,725, Table I, SEQ ID NO: 8565, p. 240.) U.S. Patent Application 09/488,725 does not disclose any additional information relating to the sequence such as information relating to the differential expression pattern of the nucleic acid.

Applicants also note that WO 01/53312 also claims priority to U.S. Patent Application 09/471,275, filed December 23, 1999. Applicants note that this application also discloses a raw nucleic acid sequence and states that it is "similar to MLN64" and "similar to I38027 (PID: g2135214)". (See U.S. Patent Application 09/471,275, Table I, SEQ ID NO: 1605, p. 77). U.S. Patent Application Serial No. 09/471,275 does not disclose any additional information relating to the sequence such as information relating to the differential expression pattern of the nucleic acid.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference.

He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the applicants filed patent applications disclosing the polypeptide of SEQ ID NO: 14 prior to the earliest priority date of the cited reference. In particular, U.S. Provisional Patent Application 60/170262 filed 12/9/1999 discloses the polypeptide of SEQ ID NO: 14, and contemplates the production of antibodies that specifically bind the polypeptide of SEQ ID NO: 14. Because Applicants demonstrated, by means of the disclosure in their provisional application filed December 9, 1999, that they were in possession of so much of the claimed invention as is disclosed in U.S. Patent Application 09/471,275 and U.S. Patent Application 09/488,725 prior to the December 23, 1999 and January 21, 2000 filing dates of these references, Applicants respectfully submit that these references are not available as prior art.

Accordingly, Applicants respectfully request that the rejections under 35 USC §102 be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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